

**Remarks/Arguments**

Claims 1 to 7 and 11 to 18 and 20 are pending in this application.

Claims 8 to 10, drawn to non-elected inventions, have been cancelled. Dependent Claim 19 has also been cancelled as being redundant with independent Claim 1. Claims 2, 17 and 18 have been amended.

The last Office Action stated that the following is a quotation of 35 U.S.C. 103(a) which forms the basis for the obviousness rejection set forth in such Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 11 to 14 and 19 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Sakuraba et al. (Chem. Pharm. Bull., Vol 43(5), (1995), pages 748-753), in view of Staszak et al. (EP 0 457 559 A2), Okeda et al. (EP 0 955 303 A2), and Antognazza et al. (U.S. 5, 907,045), individually. Applicants traverse this rejection.

The last Office Action stated that applicants claim a process of making carboxylic acid salt of compounds of formulae Ia and/or Ib comprising asymmetric hydrogenation of a carboxylic acid salt with aminoketones of formula II, in the presence of a catalyst comprising a transition metal complex of a disphosphine ligand. This is not a complete statement of even the broadest of applicants' claims – attention is drawn to (independent) Claim 1.

Under the heading "Determination of the scope and content of the prior art (MPEP 2141.01)", the last Office Action stated that Sakuraba et al. teaches a process of making HCl acid salt of compounds of formulae Ia and/or Ib comprising asymmetric hydrogenation

of an HCl acid salt with aminoketones of formula II, in the presence of a catalyst comprising a transition metal complex of a disphosphine ligand. Sakuraba et al., the primary reference, only teaches the use of HCl, a strong inorganic or mineral acid. The use of inorganic acids cause serious problems – applicants' use of carboxylic acids (certain type) unexpectedly overcame and solved such problems. A carboxylic group is  $\text{--COOH}$ .

Webster' II, New College Dictionary, (2001), states:

"carboxylic acid...an organic acid containing one or more carboxylic groups"

[Emphasis supplied] [Page 167]

Webster's Ninth New Collegiate Dictionary, (1985), states:

"carboxylic acid...an organic acid (as acetic acid) containing one or more carboxylic groups" [Emphasis supplied] [Page 206]

Applicants have defined carboxylic acid (in the specification) to mean only certain types of carboxylic acids that work within their claimed process. The specification states:

Carboxylic acids in the meaning of the present invention are carboxylic acids having one free carboxyl group which can form a salt with an amino compound of formulae II and/or I. Particularly preferred carboxylic acids are monocarboxylic acids. Dicarboxylic or tricarboxylic acids which do not form an inner salt like fumaric, maleic or adipic acid tend to give unusable resinous precipitates. However, carboxylic acids which form an inner salt and still have one free carboxy group are comprised in the definition of carboxylic acids in the meaning of the present invention. Examples of said carboxylic acids having more than one carboxy group, but having only one free carboxy group, are amino acids such as aspartic acid or glutamic acid.

[Page 4, lines 6 to 13]

So carboxylic acid in applicants' invention/specification/claims is a carboxylic acid having one free carboxylic acid.

Sakuraba et al. teaches the asymmetric hydrogenation of HCl salts. Use of such HCl salts presents a problem, as HCl is strongly acid there is a risk of decomposition while concentrating during recovery of the product (with increase amount of byproducts). Applicants' use of carboxylic acids surprisingly eliminates the problem caused by use of HCl. Carboxylic acids are less acidic than HCl.

Applicants' specification states:

In Sakuraba et al., *Chem. Pharm. Bull.* 1995, 43, 748-753, and JP-A 50-70412 the asymmetric hydrogenation of HCl salts of 3-*N*-methylamino-1-phenyl-1-propanol and 3-amino-1-phenyl-1-propanone is disclosed. EP-A-457559 discloses the preparation of HCl salts of 3-dimethylamino-1-(2-thienyl)-1-propanone and (*S*)-(-)-*N,N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine as well as the oxalate salts of (*S*)-(+)-*N,N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine and (*S*)-(-)-*N,N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine. The latter two ones being aromatic ethers of the compounds of formula I. Direct preparation of the respective organic acid salts is not disclosed in the prior art. Surprisingly, these compounds can be used in the hydrogenation reaction as well without increasing the amount of by-products. Using organic acids is favourable, since they are less acidic than HCl and therefore the risk of decomposition while concentrating during recovery of the products is reduced. The compounds obtainable by the present process can be used directly without exchange of the anion.

[Page 3, lines 8 to 19]

Sakuraba et al. and Staszak et al. do not teach or suggest the direct preparation of applicants' direct preparation of the carboxylic acid salts. Both such cited rejection references disclose only an intermediate step process. The combination of the two rejection references does not result in applicants' claimed process.

The last Office Action stated: that the difference between the instant invention and that of the prior art is that applicants use of a salt of carboxylic acid instead of a salt of HCl to prepare the corresponding salt of compounds of formula I ; and that, also, the ligands in Claims 11, 13 and 14 are different from the ligand of the prior art. This statement is incorrect as there are other important differences.

The last Office Action stated that, however, Staszak et al. teaches a similar process using HCl salts with aminoketones, wherein R1 is thienyl ring. Applicants use a direct process whereas Sakuraba et al. and Staszak et al. both use a process having an intermediate step, so use of either or both rejection references still does not achieve applicants' claimed direct process.

The last Office Action stated: that the prior art also teaches that salts of other acids such as carboxylic acids (e.g., oxalate) are applicable; and see page 5, lines 2 to 7, of Staszak et al. Applicants traverse this statement. Staszak does not say that carboxylic acids are applicable. Staszak et al. only recites five specific acids – three of which are inorganic acids. Staszak et al. recites oxalic acid and tartaric acid, both of which have two carboxylic groups, hence they are outside of applicants' claimed process and are not useful in applicants' claimed invention. Applicants' definition of carboxylic acid is a carboxylic acid that has one free carboxyl group so tartaric acid and oxalic acid are outside of applicants' claimed invention. In fact, both tartaric acid and oxalic acid direct away from applicants' claimed process because dicarboxylic acids that do not form an inter salt tend to give unusable resinous precipitates. Use of the disclosure of Staszak et al. directs away from applicants' claimed invention. Even if Sakuraba et al. and Staszak et al. are combined in the quest for applicants' claimed process, the combination does not result in (or being suggestive of) applicants' claimed process.

The last Office Action stated that Okeda et al., (pages 1 to 24, particularly, page 2, lines 11 to 15) and Antognazza et al., (col. 1 to 8) teach the ligands in Claims 11, 13 and 14 are useful for asymmetric hydrogenations reactions. This information does not make either combination rejection a basis for an obviousness rejection of applicants' claim process.

Even if Okeda et al. was combined with Sakuraba et al., the result would not be applicants' claimed process. Note that Okeda et al. does not have any specific disclosure of the area of applicants' claimed process, that it would be very complicated with little or no guidance in either rejection reference for combining them in the quest for applicants' claimed process.

Even if Antognazza et al. was combined with Sakuraba et al., the result would not be applicants' claimed process. The problem with Antognazza et al. is the same as that with Okeda et al.

The last Office Action stated that at the time the instant invention was made, workers are engaged in asymmetrical hydrogenation of an HCl acid salt with aminoketones of formula II, in the presence of a catalyst comprising a transition metal complex of a disphosphine ligand. This generic statement is not supported by any of the rejection references.

The last Office Action stated that it was not known if there was problem with salts of HCl acid but, other workers such as Staszak et al. suggest a salt of carboxylic acid is applicable. This statement is clearly incorrect – see the discussion in the specification of such problems.

The last Office Action stated that, also, note that Staszak et al. only recited two carboxylic acid and each of them lay out side of applicants' claimed process and would result in unusable resinous precipitate – nowhere did Staszak et al. refer generically or

generally to carboxylic acids. In fact, to follow Staszak et al. would result in no cure of the lousy-result two step process of Sakuaba et al.

The last Office Action stated that Okeda et al. and Antognazza et al. teach various catalysts comprising a transition metal complex of a disphosphine ligand. Nowhere do they teach or suggest that such catalyst would be useful in applicants' claimed process. Even if they did, each is only part of separate rejection in combination with Sakuraba et al.

The last Office Action has three separate rejections of the primary reference in combination with a different secondary reference. The last Office Action incorrectly treats the three secondary references as if they were part of single rejection all in with the primary rejection reference. Even if a such a combination rejection were to be made, such a rejection would fail and not result in applicants' claimed process. Okeda et al. and Antognazza et al. do not correct the defects (see above discussion of this matter) of Sakuraba et al. and Staszak et al. in the quest for applicants' claimed invention. Also, there is nothing of record to overcome the complications of each reference that hinders its combination with any or all of the three other rejection references.

There is no factual determination in the record of the level of ordinary skill in the pertinent art.

Withdrawal of this rejection is requested.

Reconsideration, reexamination and allowance of the claims are requested.

Respectfully submitted,

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Date

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